An Enantio- and Diastereoselective Synthesis of Fluorinated \( \beta \)-Aminoalkyl-oxepine Derivatives through Mannich and Ring-Closing Metathesis Reactions

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Abstract: The combination of a proline-catalyzed Mannich-type reaction between protected fluorinated aldimes and 4-pentenal followed by reduction and regioselective O-allylation gives \( \gamma \)-amino ethers that can then be used as substrates for ring-closing metathesis (RCM) reactions to afford fluorinated \( \beta \)-aminoalkyl-oxepines in a highly stereo- and enantioselective fashion. 

Key words: amino alcohols, fluorine, organocatalysis, Mannich reaction, metathesis, oxepines

Enantiopure \( \beta \)-amino acids and derivatives, such as \( \gamma \)-amino alcohols, have become appealing synthetic targets due to the fact that they are either present in or can be used as building blocks for a number of compounds with potential therapeutic properties. In fact, several of these compounds have already been shown to display antifungal, antibiotic, and cytotoxic activity. Moreover, because the presence of fluorine atoms in a potentially bioactive molecule can dramatically change not only its physical, but also its chemical properties, the preparation of fluorinated \( \beta \)-amino acids and their derivatives is also an important objective.

However, few studies have focused on the preparation of cyclic, fluorinated \( \beta \)-amino acids. Our group has previously reported on the preparation of racemic cis seven-membered \( \gamma \)\(,\gamma \)-difluorinated \( \beta \)-amino acid derivatives in a sequence that starts with imidoyl halides. These are condensed with suitable ester enolates to give intermediates that can subsequently be cyclized by means of a ring-closing olefin metathesis reaction. The product is then stereoselectively reduced to yield the desired compounds in good overall yields.

At the same time, oxygen- and nitrogen-containing heterocyclic compounds have attracted considerable attention as a result of their biological activity and their presence in a variety of natural and unnatural products. Thus, the asymmetric synthesis of oxygen heterocycles represents an important task because of the widespread occurrence of such structural motifs and their use as building blocks. Among oxygen heterocycles, seven-membered oxacycles are the central nuclei of numerous natural products. Numerous studies toward their synthesis have been reported because of their frequent natural occurrence and unusual biological properties.

We have recently reported a highly diastereo- and enantioselective approach to fluorinated \( \text{syn} \alpha \)-alkyl \( \gamma \)-amino alcohols by means of an indirect, proline-catalyzed Mannich-type reaction of fluorinated aldimes and aliphatic aldehydes. These encouraging results led us to believe that this same strategy might be used in conjunction with an RCM reaction for the preparation of fluorinated seven-membered \( \beta \)-aminoalkyl oxacycles of the type 1 (Scheme 1). Organocatalysis has become one of the key research areas in synthetic organic chemistry. Its utility in asymmetric synthesis has been amply demonstrated; moreover, it has been successfully applied to Mannich reactions, as well as many others. The RCM has also been one of the most successful methods for the preparation of medium- or large-sized rings from acyclic diene precursors. Thus, we now report on a highly diastereo- and enantioselective approach to fluorinated \( \beta \)-aminoalkyloxepines 1 by means of a synthetic strategy that uses an indirect, proline-catalyzed Mannich-type reaction of fluorinated aldimes and aliphatic aldehydes, followed by an O-allylation reaction, and finally an RCM reaction (retrosynthetic analysis, Scheme 1).

**Scheme 1**
The proline-catalyzed condensation between fluorinated imines 5a–c and 4-pentenal (6) affords the corresponding fluorinated β-amine aldehydes 4a–c in moderate yield. Since fluorinated β-amine aldehydes 4a–c are prone to epimerization, we immediately reduced them to the corresponding γ-amine alcohols 3a–c with sodium borohydride in methanol at 0 °C. Thus, fluorinated γ-amine alcohols 3a–c were obtained in moderate yields (39–50%), but with excellent diastereo- and enantioselectivities (syn:anti 96:4 and >99% ee in all three cases) (Scheme 2).

Alternatively, when the O-allyl γ-amino ether 2a was treated with Grubbs’ second-generation catalyst [(HMes)(PCy3)2Cl2Ru=CHPh] in refluxing toluene and under a set of reaction conditions that our group has recently shown to favor double bond isomerization after the RCM reaction,14 isomer 8 was obtained instead of 1a. Interestingly, this compound can also be prepared from its isomer 1a when it is subjected to the same reaction conditions (Scheme 5).

Scheme 2

For the O-allylation reaction, we decided to use sodium hydride and allyl bromide in tetrahydrofuran in the presence of 0.5 molar equivalents of tetrabutylammonium iodide (TBAI).12 Thus, when γ-amino alcohols 3a,b were treated with sodium hydride and allyl bromide in the presence of TBAI, the desired O-allyl γ-amino ethers 2a,b were obtained in excellent yields (Scheme 3) and without any detectable N-alkylation.13

Scheme 3

Finally, when O-allyl γ-amino ethers 2a,b were treated with Grubbs’ first-generation catalyst [(PCy3)2Cl2Ru=CHPh], an RCM reaction took place cleanly to afford the corresponding fluorinated β-aminalkyl oxepines 1a,b in high yield. (Scheme 4).

Scheme 4

In summary, the combination of a proline-catalyzed Mannich-type reaction between protected fluorinated aldimines and 4-pentenal, followed by reduction and O-allylation affords γ-amino ethers 2. These compounds can then be used as substrates for RCM reactions that ultimately afford seven-membered fluorinated β-aminalkyl oxacycles 1 in a highly stereo- and enantioselective fashion. To the best of our knowledge, this is the first time that compounds with this type of structure have been described in the literature.

Preparation of Fluorinated γ-Amino Alcohols 3a–c; General Procedure

To a solution of the starting fluorinated imine7 5 (1 mmol) in N-methylpyrrolidone (1 mL), l-proline (0.20 mmol) was added and the resulting solution was stirred at r.t. for 45 min. The temperature was then lowered to –20 °C and 4-pentenial (2 mmol) was added and a syringe over 1 min. The reaction was kept at –20 °C for 24 h, then at –10 °C for an additional 24 h, and finally at 0 °C for a further 24 h. The reaction mixture was then hydrolyzed by the addition of sat. aq NH4Cl solution (10 mL), followed by quick extraction with EtOAc (3 × 10 mL). The organic phases were pooled together, washed once with sat. aq NaCl (10 mL) solution, and dried over anhydrous Na2SO4. After removal of the solvent under vacuum, the crude residue was dissolved in dry MeOH (5 mL per mmol of starting fluorinated imine). The solution was cooled to 0 °C and treated with 5 mol equiv of NaBH4, after which the reaction was allowed to reach r.t. and stirred for 5 h. Then, the reaction was quenched with sat. aq NH4Cl solution and extracted into EtOAc. The organic layer was washed with brine and dried over Na2SO4. The corresponding fluorinated γ-amino alcohols 3 were isolated after silica gel column purification with hexane–EtOAc (4:1) as eluent.

Scheme 5

All solvents were distilled prior to use. 1H NMR, 19F NMR, and 13C NMR spectra were measured at 300 MHz, 282.4 MHz, and 75.5 MHz respectively, on a Bruker 300 spectrometer. IR spectra were recorded with a Thermo Nicolet 380 FT–IR infrared spectrometer. High resolution mass spectra were obtained on a VG Autospec (micromass) mass spectrometer. Column chromatography was performed on 100–200 mesh silica gel (Merck) using Hexane–EtOAc as eluent.
(S)-2-[(S)-2,2,2-Trifluoro-1-[4-(methoxyphenylamino)ethyl]pent-4-en-1-ol (3a)

Obtained in 50% yield in accordance with the general procedure described above. For complete physical and spectroscopic data of this compound, see ref. 7.

(S)-2-[(S)-2,2,2,3,3-Pentafluoro-1-[4-(methoxyphenylamino)ethyl]pent-4-en-1-ol (3b)

Obtained in 45% yield in accordance with the general procedure described above. White solid; mp 78–79 °C; [α]D23 +17.5 (c 0.77, CHCl3).


1H NMR (300 MHz, CDCl3): δ = 1.52–1.60 (m, 1 H), 1.97–2.10 (m, 1 H), 2.19–2.30 (m, 1 H), 2.34–2.45 (m, 1 H), 3.49–3.64 (m, 2 H), 3.75 (s, 3 H), 3.76–3.82 (m, 1 H), 4.43–4.57 (m, 1 H), 5.07–5.13 (m, 2 H), 5.73–5.87 (m, 1 H), 6.68 (d, J = 8.9 Hz, 2 H), 6.78 (d, J = 8.9 Hz, 2 H).

11C NMR (75.5 MHz, CDCl3): δ = 30.5 (t), 40.5 (d), 53.4 (dd, 2JCF=24.2 Hz, 20.3 Hz), 55.7 (q), 61.9 (t), 114.7 (d), 115.0 (d), 117.3 (t), 135.6 (d), 140.6 (s), 152.9 (s).

19F NMR (282.4 MHz, CDCl3): δ = –82.65 (s, 3 F), –119.03 (dd, JF–F = 273.1 Hz, JF–H = 19.9 Hz, 1 F).


Preparation of Fluorinated -Allyl Amino Ethers 2a,b; General Procedure

A solution of Grubbs first generation ruthenium catalyst (PCy3)2Ru=CPh (15 mol%) in dry CHCl3 was added via cannula to a solution of amino ethers 2a–c (0.08 mmol) in CH2Cl2 (4 mL, 0.2 M). The resulting dark brown solution was kept at r.t. until TLC indicated that the starting material was no longer present (usually 1 h). The solvents were removed under reduced pressure and the residue was purified by means of flash column chromatography on silica gel using hexane–EtOAc (9:1).

4-Methoxy-N-[(S)-2,2,2-Trifluoro-1-[(S)-2,3,4,7-tetrahydroxypent-3-yl]ethyln]aniline (1a)

Obtained in 80% yield as a yellowish oil in accordance with the general procedure described above. [α]D25 –30.5 (c 0.93, CHCl3).

IR (neat): 3607, 2925, 2854, 1736, 1716, 1513, 1365, 1231, 1128, 1036, 820, 695 cm−1.
**1H NMR** (300 MHz, CDCl3): δ = 2.40–2.51 (m, 3 H), 3.51 (d, J = 9.8 Hz, 1 H), 3.73 (s, 3 H), 3.76–3.95 (m, 3 H), 4.13–4.30 (m, 2 H), 5.65–5.78 (m, 2 H), 6.63 (d, J = 8.7 Hz, 2 H), 6.80 (d, J = 8.9 Hz, 2 H).

**13C NMR** (75.5 MHz, CDCl3): δ = 26.7 (t), 40.1 (d), 55.7 (q), 57.7 (q, 2J = 27.0 Hz), 70.3 (t), 73.2 (t), 114.9 (d), 128.6 (d), 130.1 (q, 2J = 284.8 Hz), 130.5 (d), 140.8 (s), 153.0 (s).

**19F NMR** (282.4 MHz, CDCl3): δ = –72.86 (d, J = 7.2 Hz, 3 F).

HRMS (El): m/z calculated for C13H13F4NO2: 301.1286; found: 301.1285.

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**References**


(13) In the case of γ-amino alcohol 2c, however, the yield in the O-allylation reaction was substantially lower because of competitive side reactions. As the O-allylation product turned out to be very difficult to purify, we decided not to continue with this substrate. 